IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

GEERLINGS ET AL.

Serial Number: 07/657,580 Group Art Unit: 2203

Filed: February 19, 1991 Examiner: M. Zmurko

For: RADIOIMMUNOTHERAPY USING ALPHA-PARTICLES EMISSION

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Otto A. Gansow, am co-author of the paper entitled "Targeting in Erythroleukemic Mice:Radioiodinated and Chelated Radiometal-Conjugated Monoclonal Antibody." This paper was published as part of the Proceedings of the John Jacob Able Symposium for Drug Development in 1982. We reported at the top of page 167, that "[t]ypical alpha emitters that might be bound by the chelates are radium-224, lead-212, bismuth-212, and actinium-225." These radioactive metals were listed because we believed they were chelate bindable alpha emitters. We also reported that radium-224 was a preferred alpha emitter because "it decays though four additional daughter nuclides of relatively short half life, each of which emits a high-energy alpha particle."

Thus, we recommended radium-224 because it has a relatively short half life and because it decays through four additional daughter nuclides, each of which have relatively short half lives.

Although we reported that actinium-225 was a typical alpha emitter that might be bound by a chelator, we did not recommend that actinium-225 should be selected for use at that time as an alpha emitter for therapy. The antibody technology which would make use of long-lived radionuclides desirable was not known then..

In the final paragraph on page 166 we reported chelatable radiometals having suitable characteristics that are gamma emitters and beta emitters. We mentioned that all listed radiometals with "suitable characteristics" have short half lives. We also commented that the purpose for this is that it spares the patient large doses of radiation. This comment applies as well to alpha emitters. In fact, our recommendation that radium-224 be selected conforms with our teaching that short half life radionuclides should be selected. Furthermore, short half life radionuclides fit with the IgG monoclonal antibodies used to illustrate the targeting of chelated radionuclides.

At the time the symposium took place in 1981, it was not believed that actinium was a useful alpha emitter for radiotherapy by conjugation to monoclonal antibodies. With its long half life, it was believed to give too much toxicity. It was only later when human IgM monoclonal antibodies became available and were found to be characterized by long residence times and long localization times, that it became possible to consider using the long half life alpha emitter actinium-225. In addition, human antibodies also provide the advantage that they do not have an immunogenic or antigenic presence and, therefore, are not quickly cleared by means of the patient's immune system.

Thus, it was the development of human IgM monoclonal antibodies that made it possible to consider the use of the long half life alpha emitter, actinium-225. As an example of a human IgM, the circulation time, clearance, immunogenicity and residence time of human IgM 16.88 is reported by Haisma et al. (J. Natl. Cancer Inst., 83, 1813-1819, (1991)), beginning on page 1817.

At the time of the symposium and publication of our article radionuclides useful for imaging and therapy were believed to be limited to relatively short half life isotopes. Among the alpha-emitters, actinium-225 did not meet this criterion. At that time, Actinium-225 was not considered to be an alpha emitter suitable for therapy when conjugated to a monoclonal antibody available in 1991.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Otto A. Gansow, Ph.D.

Date: 3/6/92

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